

## **SUSTAINED DELIVERY OF AN ACTIVE AGENT USING AN IMPLANTABLE SYSTEM**

### **Cross-Reference to Related Applications**

This application is a continuation-in-part application of a provisional application (serial number as yet unknown) which was filed on February 2, 1996 as regular US application Serial No. 08/595,761 and converted to a provisional application via a petition filed on January 21, 1997.

### **Technical Field**

This invention is related to the sustained delivery of a biologically active agent. More particularly, the invention is directed to an implantable delivery system for the prolonged delivery of an active agent to a fluid environment in a natural or artificial body cavity.

### **Background of the Invention**

Treatment of disease by prolonged delivery of an active agent at a controlled rate has been a goal in the drug delivery field. Various approaches have been taken toward delivering the active agents.

One approach involves the use of implantable diffusional systems. For example, subdermal implants for contraception are described by Philip D. Darney in *Current Opinion in Obstetrics and Gynecology* 1991, 3:470-476. Norplant® requires the placement of 6 levonorgestrel-filled silastic capsules under the skin. Protection from conception for up to 5 years is achieved. The implants operate by simple diffusion, that is, the active agent diffuses through the polymeric material at a rate that is controlled by the characteristics of the active agent formulation and the polymeric material. Darney further describes biodegradable implants, namely Capranor™ and norethindrone pellets.

1 These systems are designed to deliver contraceptives for about one year and  
2 then dissolve. The Capranor™ systems consist of poly( $\epsilon$ -caprolactone)  
3 capsules that are filled with levonorgestrel and the pellets are 10% pure  
4 cholesterol with 90% norethindrone.

5 Implantable infusion pumps have also been described for delivering  
6 drugs by intravenous, intra-arterial, intrathecal, intraperitoneal, intraspinal and  
7 epidural pathways. The pumps are usually surgically inserted into a  
8 subcutaneous pocket of tissue in the lower abdomen. Systems for pain  
9 management, chemotherapy and insulin delivery are described in the *BBI*  
10 *Newsletter*, Vol. 17, No. 12, pages 209-211, December 1994. These systems  
11 provide for more accurately controlled delivery than simple diffusional  
12 systems.

13 One particularly promising approach involves osmotically driven  
14 devices such as those described in U.S. Patent Nos. 3,987,790, 4,865,845,  
15 5,057,318, 5,059,423, 5,112,614, 5,137,727, 5,234,692 and 5,234,693  
16 which are incorporated by reference herein. These devices can be implanted  
17 into an animal to release the active agent in a controlled manner for a  
18 predetermined administration period. In general, these devices operate by  
19 imbibing fluid from the outside environment and releasing corresponding  
20 amounts of the active agent.

21 The above-described devices have been useful for delivering active  
22 agents to a fluid environment of use. Although these devices have found  
23 application for human and veterinary purposes, there remains a need for  
24 devices that are capable of delivering active agents, particularly potent  
25 unstable agents, reliably to a human being at a controlled rate over a  
26 prolonged period of time.

### 27 28 Summary of the Invention

29  
30 Implantable osmotic systems for delivery of an active agent to an  
31 animal are well known. Adaptation of these systems for human use raises a

1 number of difficult issues. The size of the device may need to be decreased  
2 for human implantation. The strength of the device must be sufficient to  
3 ensure a robust system. Accurate and reproducible delivery rates and  
4 durations must be ensured and the period from implantation to start-up of  
5 delivery must be minimized. The active agent must return its purity and  
6 activity for extended periods of time at the elevated temperatures  
7 encountered in the body cavity.

8         Accordingly, in one aspect, the invention is a fluid-imbibing device for  
9 delivering an active agent formulation to a fluid environment of use. The  
10 device comprises a water-swellaable, semipermeable material that is received  
11 in sealing relationship with the interior surface at one end of an impermeable  
12 reservoir. The device further contains an active agent to be displaced from  
13 the device when the water-swellaable material swells.

14         In another aspect, the invention is directed to an implantable device for  
15 delivering an active agent to a fluid environment of use. The device  
16 comprises a reservoir and a back diffusion regulating outlet in a mating  
17 relationship. The flow path of the active agent comprises a pathway formed  
18 between the mating surfaces of the back diffusion regulating outlet and the  
19 reservoir.

20         In yet another aspect, the present invention is directed to a device for  
21 storing an active agent in a fluid environment of use during a predetermined  
22 administration period, the device comprising a reservoir containing an active  
23 agent. The reservoir is impermeable and formed at least in part from a  
24 metallic material. The portion of the reservoir contacting the active agent is  
25 non-reactive with the active agent, and is formed of a material selected from  
26 the group consisting of titanium and its alloys.

27         In a further aspect, the invention is an implantable fluid-imbibing active  
28 agent delivery system that comprises an impermeable reservoir. The  
29 reservoir contains a piston that divides the reservoir into an active agent  
30 containing chamber and a water-swellaable agent containing chamber. The  
31 active agent containing chamber is provided with a back-diffusion regulating

1 outlet. The water-swellaable agent containing chamber is provided with a  
2 semipermeable plug. Either the plug or the outlet is releasable from the  
3 reservoir at an internal pressure that is lower than the maximum osmotic  
4 pressure generated by the water-swellaable agent.

5 The invention is further directed to a fluid-imbibing implantable active  
6 agent delivery system where the time to start-up of delivery is less than 10%  
7 of the predetermined administration period.

8 In another aspect, the invention is directed to a method for preparing a  
9 fluid-imbibing implantable active agent delivery system. The method  
10 comprises injection molding a semipermeable plug into the end of an  
11 impermeable reservoir such that the plug is protected by the reservoir.

12 In still another aspect, the invention is directed to an impermeable  
13 active agent delivery system for delivering an active agent that is susceptible  
14 to degradation. The reservoir contains a piston that divides the reservoir into  
15 a water-swellaable agent chamber and an active agent chamber. The open  
16 end of the water-swellaable agent chamber contains a semipermeable  
17 membrane and the open end of the active agent chamber contains a back-  
18 diffusion regulating outlet. The system effectively seals the active agent  
19 chamber and isolates it from the environment of use.

20 In a further aspect, the invention is directed to a back-diffusion  
21 regulating outlet useful in an active agent delivery system. The outlet defines  
22 a flow path wherein the length, interior cross-sectional shape and area  
23 provide for an average linear velocity of active agent that is higher than the  
24 linear inward flow of fluid in the environment of use.

25 The invention is also directed to a semipermeable plug useful in an  
26 active agent delivery system. The plug is water-swellaable and must expand  
27 linearly in the delivery system to commence pumping upon insertion of the  
28 system into the fluid environment of use.

29 The invention is further directed to implantable delivery systems useful  
30 for delivering leuprolide.

### **Description of the Drawings**

The figures are not drawn to scale, but are set forth to illustrate various embodiments of the invention. Like numbers refer to like structures.

Figs. 1 and 2 are partial cross-sectional views of two embodiments of the delivery device of the invention.

Fig. 3 is an enlarged cross-sectional view of the back-diffusion regulating outlet of Fig. 1.

Fig. 4 is a graph that shows the effect of orifice diameter and length on drug diffusion.

Figs. 5, 6, 7 and 8 are enlarged cross-sectional views of further embodiments of the semipermeable plug end of the reservoir according to the invention.

Figs. 9, 10 and 11 are graphs of release rates for systems with leuprolide (Fig. 9) and with blue dye and with different membranes (Figs. 10 and 11).

### **Detailed Description of the Invention**

The present invention provides a device for the delivery of an active agent to a fluid environment of use in which the active agent must be protected from the fluid environment until it is delivered. Prolonged and controlled delivery is achieved.

### **Definitions**

The term "active agent" intends the active agent(s) optionally in combination with pharmaceutically acceptable carriers and, optionally additional ingredients such as antioxidants, stabilizing agents, permeation enhancers, etc.

1 By a "predetermined administration period" is intended a period of  
2 greater than 7 days, often between about 30 days and 2 years, preferably  
3 greater than about 1 month and usually between about 1 month and 12  
4 months.

5 By the time to "start-up" of delivery is intended the time from insertion  
6 into the fluid environment of use until the active agent is actually delivered at  
7 a rate not less than approximately 70% of the intended steady-state rate.

8 The term "impermeable" intends that the material is sufficiently  
9 impermeable to environmental fluids as well as ingredients contained within  
10 the dispensing device such that the migration of such materials into or out of  
11 the device through the impermeable device is so low as to have substantially  
12 no adverse impact on the function of the device during the delivery period.

13 The term "semipermeable" intends that the material is permeable to  
14 external fluids but substantially impermeable to other ingredients contained  
15 within the dispensing device and the environment of use.

16 As used herein, the terms "therapeutically effective amount" or  
17 "therapeutically effective rate" refer to the amount or rate of the active agent  
18 needed to effect the desired biologic or pharmacologic effect.

19 The active agent delivery devices of the invention find use where the  
20 prolonged and controlled delivery of an active agent is desired. In many  
21 cases the active agent is susceptible to degradation if exposed to the  
22 environment of use prior to delivery and the delivery devices protect the agent  
23 from such exposure.

24 Fig. 1 shows one embodiment of the device according to the invention.  
25 In Fig. 1 a fluid-imbibing system **10** is shown that comprises an impermeable  
26 reservoir **12**. The reservoir **12** is divided into two chambers by a piston **16**.  
27 The first chamber **18** is adapted to contain an active agent and the second  
28 chamber **20** is adapted to contain a fluid-imbibing agent. A back-diffusion  
29 regulating outlet **22** is inserted into the open end of the first compartment **18**  
30 and a water-swellable semipermeable plug **24** is inserted into the open end of  
31 the second chamber **20**. In Fig. 1, the back-diffusion regulating outlet **22** is

1 shown as a male threaded member in a mating relationship with the smooth  
2 interior surface of the reservoir 12 thereby forming therebetween helical flow  
3 path 34. The pitch (x), the amplitude (y), and the cross-sectional area and  
4 shape of the helical path 34 formed between the mating surfaces of the back-  
5 diffusion regulating outlet 22 and the reservoir 12 as shown in Fig. 3 are  
6 factors that affect both the efficiency of path 34 preventing back-diffusion of  
7 external fluid into the formulation in chamber 18 and the back pressure in the  
8 device. The geometry of outlet 22 prevents water diffusion into the reservoir.  
9 In general, it is desired that these characteristics be selected so that the  
10 length of the helical flow path 34 and the velocity of flow of active agent  
11 therethrough is sufficient to prevent back-diffusion of external fluid through the  
12 flow path 34 without significantly increasing the back pressure, so that,  
13 following start-up, the release rate of the active agent is governed by the  
14 osmotic pumping rate.

15 Fig. 2 is a second embodiment of the device of the invention with a  
16 reservoir 12, piston 16 and plug 26. In this embodiment, the flow path 36 is  
17 formed between a threaded back-diffusion regulating outlet 40 and threads 38  
18 formed on the interior surface of the reservoir 12. The amplitudes of the  
19 threaded portions of the back-diffusion regulating outlet 40 and reservoir 12  
20 are different so that a flow path 36 is formed between the reservoir 12 and the  
21 back-diffusion regulating outlet 40.

22 The water-swellaable semipermeable plugs 24 and 26 shown in Figs. 1  
23 and 2 respectively are inserted into the reservoir such that the reservoir wall  
24 concentrically surrounds and protects the plug. In Fig. 1, the top portion 50 of  
25 the plug 24 is exposed to the environment of use and may form a flanged end  
26 cap portion 56 overlaying the end of reservoir 12. The semipermeable plug  
27 24 is resiliently engaged with the interior surface of the reservoir 12 and in  
28 Fig. 1 is shown to have ridges 60 that serve to frictionally engage the  
29 semipermeable plug 24 with the interior of reservoir 12. In addition, the  
30 ridges 60 serve to produce redundant circumferential seals that function  
31 before the semipermeable plug 24 expands due to hydration. The clearance

1 between ridges **60** and the interior surface of the reservoir **12** prevents  
2 hydration swelling from exerting stresses on the reservoir **12** that can result in  
3 tensile failure of the reservoir **12** or compression or shear failure of the plug  
4 **24**. Fig. 2 shows a second embodiment of the semipermeable plug **26** where  
5 the plug is injection molded into the top portion of the reservoir and where the  
6 top of the semipermeable plug **26** is flush with the top **62** of the reservoir **12**.  
7 In this embodiment, the diameter of the plug is substantially less than the  
8 diameter of the reservoir **12**. In both embodiments the plugs **24** and **26** will  
9 swell upon exposure to the fluid in body cavity forming an even tighter seal  
10 with the reservoir **12**.

11 The novel configurations of the components of the above-described  
12 embodiments provide for implantable devices that are uniquely suited for  
13 implantation into humans and can provide delivery devices which are capable  
14 of storing unstable formulations at body temperatures for extended periods of  
15 time, which devices have start-up times of less than 10% of the administration  
16 period and can be designed to be highly reliable and with predictable fail safe  
17 modes.

18 Reservoir **12** must be sufficiently strong to ensure that it will not leak,  
19 crack, break or distort so as to expel its active agent contents under stresses  
20 it would be subjected to during use while being impermeable. In particular, it  
21 should be designed to withstand the maximum osmotic pressure that could be  
22 generated by the water-swellaable material in chamber **20**. Reservoir **12** must  
23 also be chemically inert and biocompatible, that is, it must be non-reactive  
24 with the active agent formulation as well as the body. Suitable materials  
25 generally comprise a non-reactive polymer or a biocompatible metal or alloy.  
26 The polymers include acrylonitrile polymers such as acrylonitrile-butadiene-  
27 styrene terpolymer, and the like; halogenated polymers such as  
28 polytetrafluoroethylene, polychlorotrifluoroethylene, copolymer  
29 tetrafluoroethylene and hexafluoropropylene; polyimide; polysulfone;  
30 polycarbonate; polyethylene; polypropylene; polyvinylchloride-acrylic  
31 copolymer; polycarbonate-acrylonitrile-butadiene-styrene; polystyrene; and



1 the like. The water vapor transmission rate through compositions useful for  
2 forming the reservoir are reported in *J. Pharm. Sci.*, Vol. 29, pp. 1634-37  
3 (1970), *Ind. Eng. Chem.*, Vol. 45, pp. 2296-2306 (1953); *Materials*  
4 *Engineering*, Vol. 5, pp. 38-45 (1972); *Ann. Book of ASTM Stds.*, Vol. 8.02,  
5 pp. 208-211 and pp. 584-587 (1984); and *Ind. and Eng. Chem.*, Vol. 49, pp.  
6 1933-1936 (1957). The polymers are known in the *Handbook of Common*  
7 *Polymers* by Scott and Roff, CRC Press, Cleveland Rubber Co., Cleveland,  
8 OH. Metallic materials useful in the invention include stainless steel, titanium,  
9 platinum, tantalum, gold and their alloys as well as gold-plated ferrous alloys,  
10 platinum-plated ferrous alloys, cobalt-chromium alloys and titanium nitride  
11 coated stainless steel. A reservoir made from titanium or a titanium alloy  
12 having greater than 60%, often greater than 85% titanium is particularly  
13 preferred for the most size-critical applications, for high payload capability and  
14 for long duration applications and for those applications where the formulation  
15 is sensitive to body chemistry at the implantation site or where the body is  
16 sensitive to the formulation. Preferred systems maintain at least 70% active  
17 agent after 14 months at 37°C and have a shelf stability of at least about 9  
18 months, or more preferably at least about two years, at 2-8°C. Most  
19 preferably, systems may be stored at room temperature. In certain  
20 embodiments, and for applications other than the fluid-imbibing devices  
21 specifically described, where unstable formulations are in chamber 18,  
22 particularly protein and/or peptide formulations, the metallic components to  
23 which the formulation is exposed must be formed of titanium or its alloys as  
24 described above.

25 The devices of this invention provide a sealed chamber 18 which  
26 effectively isolates the formulation from the fluid environment. The reservoir  
27 12 is made of a rigid, impermeable and strong material. The water-swella-  
28 ble semipermeable plug 24 is of a lower durometer material and will conform to  
29 the shape of the reservoir to produce a liquid-tight seal with the interior of  
30 reservoir 12 upon wetting. The flow path 34 isolates chamber 18 from back-  
31 diffusion of environmental fluid. Piston 16 isolates chamber 18 from the

1 environmental fluids that are permitted to enter chamber **20** through  
2 semipermeable plugs **24** and **26** such that, in use at steady-state flow, active  
3 agent is expelled through outlet **22** at a rate corresponding to the rate at  
4 which water from the environment flows into the water-swellable material in  
5 chamber **20** through semipermeable plugs **24** and **26**. As a result, the plug  
6 and the active agent formulation will be protected from damage and their  
7 functionality will not be compromised even if the reservoir is deformed. In  
8 addition, the use of sealants and adhesives will be avoided and the attendant  
9 issues of biocompatibility and ease of manufacture resolved.

10 Materials from which the semipermeable plug are made are those that  
11 are semipermeable and that can conform to the shape of the reservoir upon  
12 wetting and adhere to the rigid surface of the reservoir. The semipermeable  
13 plug expands as it hydrates when placed in a fluid environment so that a seal  
14 is generated between the mating surfaces of the plug and the reservoir. The  
15 strength of the seals between the reservoir **12** and the outlet **22** and the  
16 reservoir **12** and the plugs **24** and **26** can be designed to withstand the  
17 maximum osmotic pressure generated by the device. In a preferred  
18 alternative, the plugs **24** and **26** may be designed to withstand at least 10X  
19 the osmotic agent compartment **20** operating pressure. In a further  
20 alternative the plugs **24** and **26** may be releasable from the reservoir at an  
21 internal pressure that is lower than the pressure needed to release the back  
22 diffusion regulating outlet. In this fail safe embodiment, the water-swellable  
23 agent chamber will be opened and depressurized, thus avoiding dispelling  
24 the diffusion regulating outlet and attendant release of a large quantity of the  
25 active agent. In other cases, where a fail-safe system requires the release of  
26 the active agent formulation rather than the water-swellable agent  
27 formulation, the semipermeable plug must be releasable at a pressure that is  
28 higher than the outlet.

29 In either case, the semipermeable plug must be long enough to  
30 sealably engage the reservoir wall under the operating conditions, that is, it  
31 should have an aspect ratio of between 1:10 and 10:1 length to diameter,

1 preferably at least about 1:2 length to diameter, and often between 7:10 and  
2 2:1. The plug must be able to imbibe between about 0.1% and 200% by  
3 weight of water. The diameter of the plug is such that it will sealingly fit inside  
4 the reservoir prior to hydration as a result of sealing contact at one or more  
5 circumferential zones and will expand in place upon wetting to form an even  
6 tighter seal with the reservoir. The polymeric materials from which the  
7 semipermeable plug may be made vary based on the pumping rates and  
8 device configuration requirements and include but are not limited to  
9 plasticized cellulosic materials, enhanced polymethylmethacrylate such as  
10 hydroxyethylmethacrylate (HEMA) and elastomeric materials such as  
11 polyurethanes and polyamides, polyether-polyamide copolymers,  
12 thermoplastic copolyesters and the like.

13 The piston 16 isolates the water-swellable agent in chamber 20 from  
14 the active agent in chamber 18 and must be capable of sealably moving  
15 under pressure within reservoir 12. The piston 16 is preferably made of a  
16 material that is of lower durometer than the reservoir 12 and that will deform  
17 to fit the lumen of the reservoir to provide a fluid-tight compression seal with  
18 the reservoir 12. The materials from which the piston are made are  
19 preferably elastomeric materials that are impermeable and include but are not  
20 limited to polypropylene, rubbers such as EPDM, silicone rubber, butyl  
21 rubber, and the like, and thermoplastic elastomers such as plasticized  
22 polyvinylchloride, polyurethanes, Santoprene<sup>®</sup>, C-Flex<sup>®</sup> TPE (Consolidated  
23 Polymer Technologies Inc.), and the like. The piston may be of a self-loading  
24 or compression-loaded design.

25 The back-diffusion regulating outlet 22 forms the delivery pathway  
26 through which the active agent flows from the chamber 18 to the implantation  
27 site where absorption of the active agent takes place. The seal between the  
28 outlet 22 and the reservoir 12 can be designed to withstand the maximum  
29 osmotic pressure generated within the device or to fail-safe in the modes  
30 described above. In a preferred embodiment, the pressure required to

1 release back-diffusion regulating outlet **22** is at least 10X the pressure  
2 required to move piston **16** and/or at least 10X the pressure in chamber **18**.

3 The exit flow path of the active agent is the pathway **34** formed  
4 between the mating surfaces of the back-diffusion regulating outlet **22** and the  
5 reservoir **12**. The pathway length, interior cross-sectional shape and area of  
6 the outlet path **34** or **36** are chosen such that the average linear velocity of  
7 the exiting active agent is higher than that of the linear inward flux of materials  
8 in the environment of use due to diffusion or osmosis, thereby attenuating or  
9 moderating back-diffusion and its deleterious effects of contaminating the  
10 interior of the pump, destabilizing, diluting, or otherwise altering the  
11 formulation. The release rate of active agent can be modified by modifying  
12 the outlet pathway geometry, which relationship is shown below.

13 The convective flow of active agent out of outlet **22** is set by the  
14 pumping rate of the system and the concentration of active agent in chamber  
15 **20** and can be represented as follows:

$$16 \quad Q_{ca} = (Q) (C_a) \quad (1)$$

17 where

18  $Q_{ca}$  is the convective transport of agent A in mg/day

19 Q is the overall convective transport of the agent and its  
20 diluents in cm<sup>3</sup>/day

21  $C_a$  is the concentration of agent A in the formulation within  
22 chamber **20** in mg/cm<sup>3</sup>

23 The diffusive flow of agent A through the material in the outlet **22** is a  
24 function of agent concentration, cross-sectional configuration of flow path **34**  
25 or **36**, agent diffusivity and length of flow path **34** or **36**, and can be  
26 represented as follows:

$$27 \quad Q_{da} = D \pi r^2 \Delta C_a / L \quad (2)$$

28 where

29  $Q_{da}$  is the diffusive transport of agent A in mg/day

30 D is the diffusivity through the material in path **34** or **36** in  
31 cm<sup>2</sup>/day

$r$  is the effective inner radius of the flow path in cm

$\Delta C_a$  is the difference between the concentration of agent A in the reservoir and in the body outside of the outlet **22** in  $\text{mg}/\text{cm}^3$

$L$  is the length of the flow path in cm

In general, the concentration of agent in the reservoir is much greater than the concentration of agent in the body outside of the orifice such that the difference,  $\Delta C_a$  can be approximated by the concentration of agent within the reservoir,  $C_a$ .

$$Q_{da} = D \pi r^2 C_a / L \quad (3)$$

It is generally desirable to keep the diffusive flux of agent at less than 10% of the convective flow. This is represented as follows:

$$Q_{da}/Q_{ca} = D \pi r^2 C_a / Q C_a L = D \pi r^2 / Q L \leq 0.1 \quad (4)$$

Equation 4 indicates that the relative diffusive flux decreases with increasing volumetric flow rate and path length and increases with increasing diffusivity and channel radius and is independent of drug concentration.

Equation 4 is plotted in Figure 4 as a function of length ( $L$ ) and diameter ( $d$ ) for  $D = 2 \times 10^{-6} \text{ cm}^2/\text{sec}$  and  $Q = 0.36 \mu\text{l}/\text{day}$ .

The diffusive flux of water where the orifice opens into chamber **18** can be approximated as:

$$Q_{wd}(\text{res}) = C_o Q e^{(-QL/D_w A)} \quad (5)$$

where

$C_o$  is the concentration profile of water in  $\text{mg}/\text{cm}^3$

$Q$  is the mass flow rate in  $\text{mg}/\text{day}$

$L$  is the length of the flow path in cm

$D_w$  is the diffusivity of water through the material in the flow path in  $\text{cm}^2/\text{day}$

A is the cross-sectional area of the flow path in  $\text{cm}^2$

The hydrodynamic pressure drop across the orifice can be calculated as follows:

$$\Delta P = \frac{8QL\mu}{\pi r^4} \quad (6)$$

Simultaneously solving equations (4), (5) and (6) gives the values shown in Table 1 where:

$$\begin{aligned} Q &= 0.38 \mu\text{l/day} \\ C_a &= 0.4 \text{ mg}/\mu\text{l} \\ L &= 5 \text{ cm} \\ D_a &= 2.00 \text{ E-06 cm}^2/\text{sec} \\ \mu &= 5.00 \text{ E} + 02 \text{ cp} \\ C_{w0} &= 0 \text{ mg}/\mu\text{l} \\ D_w &= 6.00 \text{ E} + 06 \text{ cm}^2/\text{sec} \end{aligned}$$

**Table 1**

Effective	Orifice dia (mil)	Drug Diffusion & Pumping			Water Intrusion		Pressure Drop psi
		Pump rate mg/day	Diffusion mg/day	Diff/Conv QD <sub>a</sub> /QC <sub>a</sub>	QD <sub>w</sub> mg/day	Qdw mg/year	
	Cross Sec area (mm <sup>2</sup> )	QC <sub>a</sub>	QD <sub>a</sub>	QD <sub>a</sub> /QC <sub>a</sub>	QD <sub>w</sub>	Qdw	delta P
1	0.00051	0.152	0.0001	0.0005	0	0	1.55800
2	0.00203	0.152	0.0003	0.0018	1.14E-79	4.16E-77	0.09738
3	0.00456	0.152	0.0006	0.0041	4.79E-36	1.75E-33	0.01923
4	0.00811	0.152	0.0011	0.0074	8.89E-21	3.25E-18	0.00609
5	0.01267	0.152	0.0018	0.0115	1.04E-13	3.79E-11	0.00249
6	0.01824	0.152	0.0025	0.0166	7.16E-10	2.61E-07	0.00120
7	0.02483	0.152	0.0034	0.0226	1.48E-07	5.4E-05	0.00065
8	0.03243	0.152	0.0045	0.0295	4.7E-06	0.001715	0.00038
9	0.04105	0.152	0.0057	0.0373	5.04E-05	0.018381	0.00024
10	0.05068	0.152	0.0070	0.0461	0.000275	0.100263	0.00016
11	0.06132	0.152	0.0085	0.0558	0.000964	0.351771	0.00011
12	0.07298	0.152	0.0101	0.0664	0.002504	0.913839	0.00008
13	0.08564	0.152	0.0118	0.0779	0.005263	1.921027	0.00005
14	0.09933	0.152	0.0137	0.0903	0.00949	3.463836	0.00004
15	0.11402	0.152	0.0158	0.1037	0.015269	5.573195	0.00003
16	0.12973	0.152	0.0179	0.1180	0.022535	8.225224	0.00002
17	0.14646	0.152	0.0202	0.1332	0.031114	11.35656	0.00002
18	0.16419	0.152	0.0227	0.1493	0.040772	14.88166	0.00001
19	0.18295	0.152	0.0253	0.1664	0.051253	18.70728	0.00001
20	0.20271	0.152	0.0280	0.1844	0.062309	22.7427	0.00001

The calculations indicate that an orifice diameter of between about 3 and 10 mil and a length of 2 to 7 cm is optimal for a device with the operating conditions described. In a preferred embodiment, the pressure drop across

1 the orifice is less than 10% of the pressure required to release the back-  
2 diffusion regulating outlet **22**.

3 The back-diffusion regulating outlet **22** preferably forms a helical  
4 pathway **34** or **36** incorporating a long flow path with a means of mechanically  
5 attaching the outlet into the reservoir without using adhesives or other  
6 sealants. The back-diffusion regulating outlet is made of an inert and  
7 biocompatible material selected from but not limited to metals including but  
8 not limited to titanium, stainless steel, platinum and their alloys and cobalt-  
9 chromium alloys and the like, and polymers including but not limited to  
10 polyethylene, polypropylene, polycarbonate and polymethylmethacrylate and  
11 the like. The flow path is usually between about 0.5 and 20 cm long,  
12 preferably between about 1 and 10 cm long and between about 0.001 and  
13 0.020 inches in diameter, preferably between about 0.003 and 0.015 inches  
14 to allow for a flow of between about 0.02 and 50  $\mu\text{l/day}$ , usually 0.2 to 10  
15  $\mu\text{l/day}$  and often 0.2 to 2.0  $\mu\text{l/day}$ . Additionally, a catheter or other system  
16 may be attached to the end of the back-diffusion regulating outlet to provide  
17 for delivery of the active agent formulation at a site removed from the implant.  
18 Such systems are known in the art and are described, for example, in U.S.  
19 Patent Nos. 3,732,865 and 4,340,054 which are incorporated herein by  
20 reference. Further, the flow path design may be useful in systems other than  
21 the fluid-imbibing devices specifically described herein.

22 The inventive device configurations described above also allow for a  
23 minimal period of delay from start-up to steady-state flow rate. This is  
24 accomplished in part as a result of the configuration of the semipermeable  
25 plug **24** or **26**. As water is imbibed by the semipermeable plug, it swells.  
26 Radial expansion is limited by the rigid reservoir **12**, thus the expansion must  
27 occur linearly, thereby pushing against the water-swellable agent in chamber  
28 **18**, which in turn pushes against the piston **16**. This allows pumping to  
29 commence prior to the time that water reaches the water-swellable agent  
30 which otherwise would be required before pumping could commence. To  
31 facilitate reliable start-up, the flow path **34** can be precharged with the active

1 agent in chamber **18**. Further, the geometry of the outlet **22** allows for initial  
2 delivery that is influenced by the concentration gradient of drug along the  
3 length of the outlet. The start-up period is less than about 25% of the  
4 predetermined delivery period and is often less than about 10% and usually  
5 less than about 5% of the predetermined delivery period. In a preferred  
6 embodiment for a one year system, at least 70% of the steady-state flow rate  
7 is achieved by day 14.

8 The water-swellaable agent formulation in chamber **20** is preferably a  
9 tissue tolerable formulation whose high osmotic pressure and high solubility  
10 propels the active agent over a long period of time while remaining in  
11 saturated solution in the water admitted by the semipermeable membrane.  
12 The water-swellaable agent is preferably selected for tolerability by  
13 subcutaneous tissue, at least at pumping rates and hypothetically resulting  
14 concentrations to allow inadvertent dispensing from implanted devices left in  
15 the patient for a longer than labeled period. In preferred embodiments, the  
16 water-swellaable agent should not diffuse or permeate through the  
17 semipermeable plug **24** or **26** to any appreciable amount (e.g., less than 8%)  
18 under normal operating conditions. Osmotic agents, such as NaCl with  
19 appropriate tableting agents (lubricants and binders) and viscosity modifying  
20 agents, such as sodium carboxymethylcellulose or sodium polyacrylate are  
21 preferred water-swellaable agents. Other osmotic agents useful as the water-  
22 swellaable agent include osmopolymers and osmagents and are described, for  
23 example, in U.S. Patent No. 5,413,572 which is incorporated by reference  
24 herein. The water-swellaable agent formulation can be a slurry, a tablet, a  
25 molded or extruded material or other form known in the art. A liquid or gel  
26 additive or filler may be added to chamber **20** to exclude air from spaces  
27 around the osmotic engine. Exclusion of air from the devices should mean  
28 that delivery rates will be less affected by nominal external pressure changes  
29 (e.g.,  $\pm 7$  p.s.i. ( $\pm 5$  a.t.m.)).

30 The devices of the invention are useful to deliver a wide variety of  
31 active agents. These agents include but are not limited to pharmacologically



1 active peptides and proteins, genes and gene products, other gene therapy  
2 agents, and other small molecules. The polypeptides may include but are not  
3 limited to growth hormone, somatotropin analogues, somatomedin-C,  
4 Gonadotropic releasing hormone, follicle stimulating hormone, luteinizing  
5 hormone, LHRH, LHRH analogues such as leuprolide, nafarelin and  
6 goserelin, LHRH agonists and antagonists, growth hormone releasing factor,  
7 calcitonin, colchicine, gonadotropins such as chorionic gonadotropin,  
8 oxytocin, octreotide, somatotropin plus an amino acid, vasopressin,  
9 adrenocorticotrophic hormone, epidermal growth factor, prolactin,  
10 somatostatin, somatotropin plus a protein, cosyntropin, lypressin,  
11 polypeptides such as thyrotropin releasing hormone, thyroid stimulation  
12 hormone, secretin, pancreaticozym, enkephalin, glucagon, endocrine agents  
13 secreted internally and distributed by way of the bloodstream, and the like.  
14 Further agents that may be delivered include  $\alpha_1$  antitrypsin, factor VIII, factor  
15 IX and other coagulation factors, insulin and other peptide hormones, adrenal  
16 cortical stimulating hormone, thyroid stimulating hormone and other pituitary  
17 hormones, interferon  $\alpha$ ,  $\beta$ , and  $\delta$ , erythropoietin, growth factors such as  
18 GCSF, GMCSF, insulin-like growth factor 1, tissue plasminogen activator,  
19 CD4, dDAVP, interleukin-1 receptor antagonist, tumor necrosis factor,  
20 pancreatic enzymes, lactase, cytokines, interleukin-1 receptor antagonist,  
21 interleukin-2, tumor necrosis factor receptor, tumor suppresser proteins,  
22 cytotoxic proteins, and recombinant antibodies and antibody fragments, and  
23 the like.

24 The above agents are useful for the treatment of a variety of conditions  
25 including but not limited to hemophilia and other blood disorders, growth  
26 disorders, diabetes, leukemia, hepatitis, renal failure, HIV infection, hereditary  
27 diseases such as cerbrosidase deficiency and adenosine deaminase  
28 deficiency, hypertension, septic shock, autoimmune diseases such as  
29 multiple sclerosis, Graves disease, systemic lupus erythematosus and  
30 rheumatoid arthritis, shock and wasting disorders, cystic fibrosis, lactose

1 intolerance, Crohn's diseases, inflammatory bowel disease, gastrointestinal  
2 and other cancers.

3       The active agents may be anhydrous or aqueous solutions,  
4 suspensions or complexes with pharmaceutically acceptable vehicles or  
5 carriers such that a flowable formulation is produced that may be stored for  
6 long periods on the shelf or under refrigeration, as well as stored in an  
7 implanted delivery system. The formulations may include pharmaceutically  
8 acceptable carriers and additional inert ingredients. The active agents may  
9 be in various forms, such as uncharged molecules, components of molecular  
10 complexes or pharmacologically acceptable salts. Also, simple derivatives of  
11 the agents (such as prodrugs, ethers, esters, amides, etc.) which are easily  
12 hydrolyzed by body pH, enzymes, etc., can be employed.

13       It is to be understood that more than one active agent may be  
14 incorporated into the active agent formulation in a device of this invention and  
15 that the use of the term "agent" in no way excludes the use of two or more  
16 such agents. The dispensing devices of the invention find use, for example,  
17 in humans or other animals. The environment of use is a fluid environment  
18 and can comprise any subcutaneous position or body cavity, such as the  
19 peritoneum or uterus, and may or may not be equivalent to the point of  
20 ultimate delivery of the active agent formulation. A single dispensing device  
21 or several dispensing devices can be administered to a subject during a  
22 therapeutic program. The devices are designed to remain implanted during a  
23 predetermined administration period. If the devices are not removed following  
24 the administration, they may be designed to withstand the maximum osmotic  
25 pressure of the water-swellable agent or they may be designed with a bypass  
26 to release the pressure generated within the device.

27       The devices of the present invention are preferably rendered sterile  
28 prior to use, especially when such use is implantation. This may be  
29 accomplished by separately sterilizing each component, e.g., by gamma  
30 radiation, steam sterilization or sterile filtration, then aseptically assembling

1 the final system. Alternatively, the devices may be assembled, then  
2 terminally sterilized using any appropriate method.

### 3 4 **Preparation of the Devices of the Invention**

5  
6 Reservoir **12** is prepared preferably by machining a metal rod or by  
7 extrusion or injection molding a polymer. The top portion of the reservoir may  
8 be open as shown in Fig. 1 or may contain a cavity as shown in Fig. 2.

9 Where the reservoir **12** is open as shown in Fig. 1, a water-swella-  
10 ble plug **24** is inserted mechanically from the outside of the  
11 reservoir without using an adhesive before or after insertion of the piston and  
12 water-swella- ble agent formulation. Reservoir **12** may be provided with  
13 grooves or threads which engage ribs or threads on plug **24**.

14 Where the reservoir **12** contains a cavity as shown in Fig. 2, the cavity  
15 may be cylindrical in shape, as shown in Fig. 5, it may be stepped, as shown  
16 in Fig. 6, it may be helical, as shown in Fig. 7 or it may be in a spaced  
17 configuration, as shown in Fig. 8. The semipermeable plug **26** is then  
18 injected, inserted, or otherwise assembled into the cavity so that it forms a  
19 seal with the reservoir wall.

20 Following insertion of the plug **26** either mechanically, by welding or by  
21 injection, the water-swella- ble agent is assembled into the reservoir followed  
22 by insertion of the piston, with appropriate steps taken to vent entrapped air.  
23 The active agent is filled into the device using a syringe or a precision  
24 dispensing pump. The diffusion moderator is inserted into the device, usually  
25 by a rotating or helical action, or by axial pressing.

26 The following examples are illustrative of the present invention. They  
27 are not to be construed as limiting the scope of the invention. Variations and  
28 equivalents of these examples will be apparent to those of skill in the art in  
29 light of the present disclosure, the drawings and claims herein.

## Examples

### Example 1 - Preparation of a Device with an HDPE Reservoir

A system containing leuprolide acetate for the treatment of prostate cancer was assembled from the following components:

Reservoir (HDPE) (5 mm outside diameter, 3 mm inside diameter)

Piston (Santoprene®)

Lubricant (silicone medical fluid)

Compressed osmotic engine (60% NaCl, 40% sodium carboxymethyl cellulose)

Membrane plug (Hytrel polyether-ester block copolymer, injection molded to desired shape)

Back diffusion Regulating Outlet (polycarbonate)

Active agent (0.78g of 60% propylene glycol and 40% leuprolide acetate)

### Assembly

The piston and inner diameter of the reservoir were lightly lubricated with silicon medical fluid. The piston **16** was inserted into the open end of chamber **20**. Two osmotic engine tablets (40 mg each) were then inserted on top of piston **16**. After insertion, the osmotic engine was flush with the end of the reservoir. The membrane plug **24** was inserted by lining up the plug with the reservoir and pushing gently until the plug was fully engaged in the reservoir. Active agent was loaded into a syringe which was then used to fill chamber **18** from its open end by injecting the material into the open tube until the formulation was ~3 mm from the end. The filled reservoir was centrifuged (outlet end "up") to remove any air bubbles that have been trapped in the formulation during filling. The outlet **22** was screwed into the open end of the reservoir until completely engaged. As the outlet was screwed in, excess formulation exited out of the orifice ensuring a uniform fill.

### Example 2 - Insertion of the Device of Example 1

Insertion of the device of Example 1 is done under aseptic conditions using a trocar similar to that used in the implantation of Norplant<sup>®</sup> contraceptive implants to position the device under the skin. The insertion area is typically in the inside of the upper arm, 8 to 10 cm above the elbow.

The area is anesthetized and an incision is made through the skin. The incision is approximately 4 mm long. The trocar is inserted into the incision until the tip of the trocar is at a distance of 4 to 6 cm from the incision. The obturator is then removed from the trocar and the device of Example 1 inserted into the trocar. The device is then advanced to the open end of the trocar using the obturator. The obturator is then held in position, thus immobilizing the device of Example 1 while the trocar is withdrawn over both the device and the obturator. The obturator is then removed, leaving the implant behind in a well-controlled position. The edges of the incision are then secured with a skin closure. The area is covered and kept dry for 2 to 3 days.

### Example 3 - Removal of the Device of Example 1

The device of Example 1 is removed as follows: The device is located by fingertip palpation of the upper arm area. The area at one end of the implant is then anesthetized and an approximately 4 mm, perpendicular incision is made through the skin and any fibrous capsule tissue surrounding the implant area. The end of the device opposite the incision is pushed so that the device end proximal to the incision is urged out of the incision. Any further fibrotic tissue is cut with a scalpel. Following removal, the procedure of Example 2 can be followed to insert a new device.

#### Example 4 - Delivery Rate of the Device of Example 1

Glass test tubes were filled with 35 ml distilled water and then placed in a 37°C water bath. A single device as described in Example 1 was placed in each test tube and the test tubes were changed periodically. The delivery rate profile from the system is shown in Fig. 9. The system does not have any start-up time because the system exhibits a period of initial high release followed by a lower steady state release for a period of 200 days.

#### Example 5 - Delivery Rate Profiles

Glass test tubes were filled with 35 ml distilled water which were then placed in a 37°C water bath. After the test tubes had come up to temperature, a single device as described in Example 1, but with membrane materials described below and containing 1% FD&C blue dye in water as the drug formulation, was placed in each tube. Water from the test tube permeated through the membrane causing the system to pump formulation (blue dye) into the surrounding water in the test tube. At regular intervals, systems were switched to fresh test tubes. The amount of dye released was determined by measuring the concentration of blue dye in each test tube using a spectrophotometer. The pumping rate was calculated from the total dye released, the volume of water in the tube, the initial concentration of dye and the interval over which the system was in the test tube. Results for two different tests are shown in Figures 10 and 11. Figure 10 shows 3 different systems with different plug materials (Hytrel® 2, 3 and 12 month systems) and Figure 11 shows 4 systems with different plug materials. These materials are:

<u>Membrane</u>	<u>Material</u>
1 month	Pebax 25 (Polyamide)
2 month	Pebax 22 (Polyamide)
3 month	Polyurethane (HP60D)
12 month	Pebax 24 (Polyamide)

1           The systems were capable of delivering for a period of from 2 to 12  
2 months, depending on the membrane used.

3  
4           **Example 6 - Preparation of a Delivery Device with a Titanium Reservoir**

5  
6           A system containing leuprolide acetate for the treatment of prostate  
7 cancer was assembled from the following components:

8           Reservoir (Titanium, Ti6Al4V alloy ) (4 mm outside diameter, 3 mm  
9           inside diameter)

10          Piston (C-Flex<sup>®</sup>)

11          Lubricant (silicone medical fluid)

12          Compressed osmotic engine (76.4% NaCl, 15.5% sodium  
13                  carboxymethyl cellulose, 6% povidone, 0.5% Mg Stearate, 1.6%  
14                  water)

15          PEG 400 (8 mg added to osmotic engine to fill air spaces)

16          Membrane plug (polyurethane polymer, injection molded to desired  
17                  shape)

18          Back diffusion Regulating Outlet (polyethylene)

19          Drug formulation (0.150g of 60% water and 40% leuprolide acetate)

20          **Assembly**

21           The piston and inner diameter of the reservoir were lightly lubricated.  
22           The piston was inserted ~0.5 cm into the reservoir at the membrane end.  
23           PEG 400 was added into the reservoir. Two osmotic engine tablets (40 mg  
24           each) were then inserted into the reservoir from the membrane end. After  
25           insertion, the osmotic engine was flush with the end of the reservoir. The  
26           membrane plug was inserted by lining up the plug with the reservoir and  
27           pushing gently until the retaining features of the plug were fully engaged in  
28           the reservoir. Formulation was loaded into a syringe which was then used to  
29           fill the reservoir from the outlet end by injecting formulation into the open tube  
30           until the formulation was ~3 mm from the end. The filled reservoir was  
31           centrifuged (outlet end "up") to remove any air bubbles that have been

trapped in the formulation during filling. The outlet was screwed into the open end of the reservoir until completely engaged. As the outlet was screwed in, excess formulation exited out of the orifice ensuring a uniform fill.

#### Example 7 - Preparation of a Leuprolide Acetate Delivery Device with a Titanium Reservoir

A system containing leuprolide acetate for the treatment of prostate cancer was assembled from the following components:

Reservoir (Titanium Ti6Al4V alloy) (4 mm outside diameter, 3 mm inside diameter, 4.5 cm length)

Piston (C-Flex® TPE elastomer, available from Consolidated Polymer Technologies, Inc.)

Lubricant (silicone medical fluid 360)

Compressed osmotic engine tablet (76.4% NaCl, 15.5% sodium carboxymethyl cellulose, 6% povidone, 0.5% Mg Stearate, 1.5% water, 50 mg total)

PEG 400 (8 mg added to osmotic engine to fill air spaces)

Membrane plug (polyurethane polymer 20% water uptake, injection molded to desired shape 3 mm diameter X 4 mm length)

Back-diffusion Regulating Outlet (polyethylene, with 6 mil X 5 cm channel)

Drug formulation (leuprolide acetate dissolved in DMSO to a measured content of 65 mg leuprolide)

#### Assembly

Systems were assembled as in Example 6, using aseptic procedures to assemble  $\gamma$ -irradiated subassemblies and filled aseptically with sterile filtered leuprolide DMSO formulation.

#### Release Rate

These systems delivered about 0.35  $\mu$ L/day leuprolide formulation containing on average 150  $\mu$ g leuprolide in the amount delivered per day.



1 They provide delivery of leuprolide at this rate for at least one year. The  
2 systems achieved approximately 70% steady-state delivery by day 14.

### 3 Implantation and Removal

4 Systems will be implanted under local anesthetic and by means of an  
5 incision and trocar as in Example 2 to patient suffering from advanced  
6 prostatic cancer.

7 After one year, systems will be removed under local anesthetic as  
8 described in Example 3. New systems may be inserted at that time.

### 9 10 Example 8 - Treatment of Prostatic Cancer

11  
12 Leuprolide acetate, an LHRH agonist, acts as a potent inhibitor of  
13 gonadotropin secretion when given continuously and in therapeutic doses.  
14 Animal and human studies indicate that following an initial stimulation, chronic  
15 administration of leuprolide acetate results in suppression of testicular  
16 steroidogenesis. This effect is reversible upon discontinuation of drug  
17 therapy. Administration of leuprolide acetate has resulted in inhibition of the  
18 growth of certain hormone-dependent tumors (prostatic tumors in Noble and  
19 Dunning male rats and DMBA-induced mammary tumors in female rats) as  
20 well as atrophy of the reproductive organs. In humans, administration of  
21 leuprolide acetate results in an initial increase in circulating levels of  
22 luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a  
23 transient increase in levels of the gonadal steroids (testosterone and  
24 dihydrotestosterone in males). However, continuous administration of  
25 leuprolide acetate results in decreased level of LH and FSH. In males,  
26 testosterone is reduced to castrate levels. These decreases occur within two  
27 to six weeks after initiation of treatment, and castrate levels of testosterone in  
28 prostatic cancer patients have been demonstrated for multiyear periods.  
29 Leuprolide acetate is not active when given orally.

1           Systems will be prepared as in Example 7, then inserted as described.  
2   The continuous administration of leuprolide for one year using these systems  
3   will reduce testosterone to castrate levels.

4           The above description has been given for ease of understanding only.  
5   No unnecessary limitations should be understood therefrom, as modifications  
6   will be obvious to those skilled in the art.